Critical Care

REVIEW

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Adjuvant therapies for management of hemorrhagic shock: a narrative review

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Abstract

Background Severe bleeding remains a leading cause of death in patients with major trauma, despite improvements in care during the acute phase, especially the application of damage control concepts. Death from hemorrhage occurs rapidly after the initial trauma, in most cases before the patient has had a chance to reach a hospital. Thus, the development of adjuvant drugs that would increase the survival of injured patients is necessary. Among the many avenues of research in this area, one is to improve cell survival during tissue hypoxia. During hemorrhagic shock, oxygen delivery to cells decreases and, despite increased oxygen extraction, anaerobic metabolism occurs, leading to acidosis, coagulopathy, apoptosis, and organ dysfunction.

Methods We selected six treatments that may help cells cope with this situation and could be used as adjuvant therapies during the initial resuscitation of severe trauma patients, including out-of-hospital settings: niacin, thiazolidinediones, prolyl hydroxylase domain inhibitors, O-GlcNAcylation stimulation, histone deacetylase inhibitors, and adenosine–lidocaine–magnesium solution. For each treatment, the biological mechanism involved and a systematic review of its interest in hemorrhagic shock (preclinical data and human clinical trials) are presented.

Conclusion Promising molecules, some of which are already used in humans for other indications, give us hope for human clinical trials in the field of hemorrhagic shock in the near future.

Background

Severe traumatic injuries are responsible for 4.4 million deaths worldwide each year, which represents 8% of all deaths [1]. Hemorrhage accounts for 35–40% of these deaths, making it the second leading cause of death from trauma after direct injury to the central nervous system [2]. Death from hemorrhage is a rapid process that occurs quickly after the initial trauma, before the patient has had a chance to reach a hospital. Therefore, management must be rapid, with interventions that do not delay surgery. These procedures focus on stopping external bleeding and include extensive use of hemostatic dressings and tourniquets, with constant concern for their re-evaluation [3]; early aggressive hypothermia control; use of the antifibrinolytic agent tranexamic acid; early management of hypocalcemia; and protocolized use of blood transfusions. This is known as the damage control strategy [4]. However, the issue of time remains a primary consideration. The time to reach a hospital remains an independent factor in mortality, even in high-income countries [5].

Without questioning the principles of damage control, the development of effective, easy-to-use, adjuvant treatments to improve the survival of casualties appears to be necessary. Many researchers are currently

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conducting studies of transfusion therapies to enhance existing blood products or develop alternatives [6, 7]. Counteracting coagulopathy or the inflammatory processes associated with severe trauma are other promising strategies [8, 9]. Another avenue of research is to improve cell survival during tissue hypoxia, which occurs in hemorrhagic shock (HS). During HS, the oxygen supply to cells decreases and, despite increased oxygen extraction, anaerobic metabolism sets in, leading to acidosis, coagulopathy, apoptosis, and organ dysfunction [10]. In this review, we focus on molecules that could help cells cope with this situation and be used in adjuvant treatments for the initial resuscitation of severe trauma patients.

Methodology

We performed a review of the literature using the PubMed scientific database using the MeSH terms "Shock, Hemorrhagic/drug therapy." The search yielded 864 articles published since the year 2000. We refined the search by excluding articles dealing with medical devices, and then further narrowed it down by excluding articles on transfusion therapy, steroid treatment, or that specifically targeted coagulation improvement or inflammation. The studies specifically focusing on management of traumatic brain injury were also excluded, although those addressing it in the context of HS were considered. We selected molecules specifically studied in the context of HS that promote cell survival during tissue hypoxia and can be used in the pre-hospital setting. We then met to select six molecules that we deemed suitable for future human clinical trials in HS given the preclinical results already obtained in animals, particularly those that have a demonstrated effect on survival. We chose niacin, thiazolidinediones, prolyl hydroxylase domain inhibitors (PHDis), O-GlcNAcylation, valproic acid (VPA), and adenosine–lidocaine–magnesium (ALM) solution. We then searched the scientific database PubMed and ClinicalTrials.gov for these six molecules and, to be exhaustive, cross-referenced the references of the initially selected articles. We have included data from preclinical work on animal models through to human research.

Results

Enhancing mitochondrial function

As the organelle responsible for producing cellular energy, mitochondria are the first to be affected by hypoxia. This results in a rapid decline in adenosine triphosphate (ATP) levels, an increase in reactive oxygen species, and the leakage of mitochondrial proteins into the cytoplasm, which ultimately leads to apoptosis [11]. In severely ill patients in septic shock, muscle biopsies have shown an association between mitochondrial dysfunction, as assessed by levels of reduced glutathione, and mortality [12]. Conversely, activation of mitochondrial biogenesis in such patients is associated with improved survival [13]. Although not as well studied in severe bleeding as it is in septic shock, mitochondrial dysfunction appears to play an important role in the pathophysiology of HS [14]. Therefore, improving mitochondrial function in the acute phase is an area of research for the management of severe trauma [10].

Niacin (Table 1)

Biological rationale Niacin is the precursor of pyrimidine nucleotides nicotinamide adenine dinucleotide (NAD), including NAD + and the reduced form NADH, and nicotinamide adenine dinucleotide phosphate (NADP), including NADP + and the reduced form NADPH. More than 500 redox reactions depend on these molecules, including mitochondrial oxidative phosphorylation and glycolysis. The NAD concentration is known to decrease in cells during HS [20]. Therefore, the hypothesis that intake of niacin or its derivatives could improve survival was tested.

Summary of preclinical works Pretreatment with nicotinamide mononucleotide, an NAD precursor derived from niacin, in rats exposed to HS results in a decrease in interleukin 6 (IL-6) and venous lactates, and in the preservation of mitochondrial respiration assessed by high-resolution respirometry. All of these results are accompanied by an increase in survival, even when treatment is administered after initiation of HS [16–18]. Mitochondrial activity is restored, as evidenced by improvement in the NAD/NADH ratio and sirtuin 1 activity in cardiac cells, and the inflammatory response, notably the NF-κB pathway, is inhibited [16, 17].

Niacin also exerts its own action by binding to receptors expressed on immune cells, notably Gpr109a (also known as HCA2), thereby mediating anti-inflammatory effects [21]. The pathway of this receptor seems to contribute to the beneficial effect of niacin in HS [16].

A study on cardiac arrest reported a better rate of return of spontaneous circulation in mice treated with the amide form of niacin, nicotinamide, and improved cardiomyocyte contractility with nicotinamide in vitro [19]. Niacin has also shown interesting results in HS in combination with other molecules, such as niacin-dichloroacetate-resveratrol, with increased survival in the absence of resuscitation and at lower doses than if each drug was administered individually [15].

Use in humans Niacin is a long-known vitamin referred to as vitamin B3 or PP (pellagra preventive). Its deficiency is the cause of pellagra, and it was used for its hypolipidemic

Table 1 Summary of niacin testing in hemorrhagic shock models

Niacin				
Current use in humans	Treatment of Pellagra Lipid-lowering agent			
Supposed mechanism of action involved in hemorrhagic shock	Precursor of NAD and NADP, coenzymes involved in mitochondrial oxidative phosphorylation and glycolysis Gpr109a receptor agonist			
Demonstrated effects in hemorrhagic shock	Murine model	Preserves mitochondrial function	Preserves NAD level in tissues	Sims et al. 2018 [15] Subramani et al. 2019 [16] Jeong et al. 2015 [17]
			Preserves ATP level in tissues	Sims et al. 2018 [18] Subramani et al. 2019 [16]
			Limits lactate increase	Sims et al. 2018 [18] Subramani et al. 2019 [16] Jeong et al. 2015 [17]
		Anti-inflammatory effect	Downregulates the nuclear factor κ B (NF-κ B) pathway	Subramani et al. 2019 [16] Jeong et al. 2015 [17]
			Limits IL-6 increase in tissues	Subramani et al. 2019 [16] Jeong et al. 2015 [17]
			Limits serum IL-6 increase	Sims et al. 2018 [18] Jeong et al. 2015 [17]
		In association with resveratrol and dichloroacetate (NiDaR):	Limits IL-6 increase in tissues Limits serum IL-6 increase	Chu et al. 2019 [15]
	Porcine model	None		
Demonstrated beneficial effect on survival in hemorrhagic shock	Murine model	Survival improvement in pretreatment or given after shock induction		Sims et al. 2018 [18] Subramani et al. 2019 [16] Jeong et al. 2015 [17]
		Survival improvement in association with resveratrol and dichloroacetate (NiDaR) in pretreatment		Chu et al. 2019 [15]
	Porcine model	None		
Other effects of interest in severe trauma management	Improvement of the rate of return of spontaneous circulation in experiments with cardiac arrest in the mouse model			Zhu et al. 2023 [19]
Clinical trials in human severe trauma	None			

NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; ATP, adenosine triphosphate; IL-6, interleukin 6

effect before the discovery of statins. Niacin is a readily available, inexpensive dietary supplement already approved for use in humans, which could facilitate clinical trials. Niacin has few side effects in routine clinical practice, the most commonly reported being itching, especially of the face [22]. Toxicity studies are still required before clinical trials can be conducted. The doses utilized in the aforementioned studies (approximately 10 mg/kg intravenously and 300–1000 mg/kg orally) differ from those used in humans. For the treatment of pellagra, the recommended intravenous dose is 500 mg over 24 h. For oral daily intake, progressively increasing from 250 mg is recommended.

Thiazolidinediones (or glitazones) (Table 2)

Biological rationale The most documented mechanism of action of thiazolidinediones is to bind peroxisome proliferator-activated receptor gamma (PPAR-γ), a transcription factor belonging to the nuclear receptor superfamily. The PPAR-γ pathway is involved in inflammatory processes [33] and plays a role in mitochondrial biogenesis, especially through PPAR-γ co-activator 1 alpha (PGC1α), which is deemed a master regulator of mitochondrial biogenesis [34, 35]. Thiazolidinediones have an effect on mitochondrial biogenesis [31, 36]. In humans, this is one avenue of research into neurodegenerative diseases [34]. As improved mitochondrial function could favor cell survival during HS, these compounds have been tested in this context.

Summary of preclinical works Thiazolidinediones appear to have protective effects against ischemia–reperfusion injury during HS. Ciglitazone reduces apoptosis markers in the liver and lungs during HS in rats

Table 2 Summary of thiazolidinedione testing in hemorrhagic shock models

Thiazolidinediones			
Current use in humans	Management and treatment of type 2 diabetes mellitus		
Supposed mechanism of action involved in HS	Proliferator-activated receptor gamma agonist		
Demonstrated effects in HS	Murine model	Anti-inflammatory effect: limitation in serum TNF-α, IL-6, and MCP-1 increase	Yang et al. 2011 [23]
		Protection effect against ischemia–reperfusion injuries	Chima et al. 2010 [24] Zingarelli et al. 2010 [25] Abdelrahman et al. 2004 [26] Collin et al. 2004 [27]
	Porcine model	None	
Demonstrated beneficial effect on survival in HS	Murine model	Survival improvement in animals treated after shock induction	Yang et al. 2011 [23]
	Porcine model	None	
Other effects of interest in severe trauma management	Stimulation of mitochondria biogenesis		Wilson-Fritch et al. 2003 [28] Fujisawa et al. 2009 [29] Bogacka et al. 2005 [30] Zhang et al. 2021 [31]
	Stimulation of mitochondria function in vitro		Wu et al. 2009 [32]
Clinical trials in human severe trauma	None		

HS, hemorrhagic shock; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; MCP-1, monocyte chemotactic protein 1

[24, 25]. The same results were obtained with 15d-PGJ2, another PPAR-γ receptor ligand [26]. Finally, in a mouse model of HS, rosiglitazone reduced inflammatory markers TNF-alpha, IL-6, and monocytic chemotactic protein (MCP)-1; decreased organ damage; and, most importantly, improved survival in treated animals [23].

The mechanisms underlying the effects of thiazolidinediones are only partially understood [37]. Certainly, the anti-inflammatory action of thiazolidinediones may play a role in their beneficial effects during HS [38, 39], but the potential preservative effect of these compounds on mitochondrial function may also be involved. Thiazolidinediones stimulate biogenesis, but it may not be the primary effect, as it takes hours to be observed [34, 35]. Rosiglitazone normalized mitochondrial membrane potential and prevented apoptotic signaling after ischemia–reperfusion injury in an in vitro study [32]. In addition to HS, PPAR-γ appears to play an important role in the development of ischemia–reperfusion injury in several models, including HS [27, 40], and thiazolidinediones have shown protective effects in this context in kidney, liver, brain, and heart tissues [27, 40, 41]. Beneficial effects of these compounds in major bleeding may also be partially mediated by this mechanism.

In summary, animal models show that Thiazolidinediones may stimulate mitochondrial biogenesis, reduce inflammation, and attenuate ischemia–reperfusion lesions in organs.

Use in humans Thiazolidinediones, chief among which are rosiglitazone and pioglitazone, are products that have already been approved and used for many years, with great tolerance, [42] to treat type 2 diabetes mellitus because they increase insulin sensitivity. This should facilitate clinical trials in HS. However, there are none at present.

Enhancing the cellular stress response

Prolyl hydroxylase domain inhibitors (Table 3)

Biological rationale PHDis increase levels of hypoxia-inducible factors (HIFs), transcription factors expressed in response to cellular hypoxia. When exposed to hypoxic stress, the cell stabilizes its HIF levels by reducing their degradation, resulting in modulation of the cellular response to hypoxia and facilitating adaptive processes to a lack of oxygen [45]. HIFs are made up of two subunits. The α subunit is continuously synthesized and degraded by prolyl hydroxylase using oxygen as a cofactor. Therefore, it does not accumulate under normoxic conditions [46, 47]. Thus, a PHDi increases the HIF-α levels in the cell by inhibiting prolyl hydroxylase. PHDis have also been shown to act on carbohydrate metabolism by activating neoglucogenesis from lactate in the Cori cycle [48]. Thus, they could accelerate lactate clearance. The action of PHDis towards HIF-α and lactate levels has led to the hypothesis that these molecules could have a beneficial effect on cellular hypoxia, particularly in the context of HS.

Table 3 Summary of prolyl hydroxylase domain inhibitors testing in hemorrhagic shock models

Prolyl hydroxylase domain inhibitors			
Current use in humans	Stimulating effect on erythropoietin secretion used in chronic renal failure Nonformulary use: treatment of iatrogenic lactic acidosis (especially metformin-induced)		
Supposed mechanism of action involved in hemorrhagic shock	Increase of HIF-α level in the cell Activation of neoglucogenesis from lactate (Cori cycle)		
Demonstrated effects in hemorrhagic shock	Murine model	Limitation in lactate increase Improvement in hemodynamic parameters Decreased prothrombin time	Wu et al. 2024 [43]
	Porcine model	None	
Demonstrated beneficial effect on survival in hemorrhagic shock	Murine model	Survival improvement in animals treated after shock induction With maintained effects during whole blood resuscitation	Wu et al. 2024 [43]
	Porcine model	None	
Other effects of interest in severe trauma management	Stimulation of axon regeneration after spinal cord experimental trauma		Li et al. 2019 [44]
Clinical trials in human severe trauma	None		

HIF-α, hypoxia inducible factor α subunit

Summary of preclinical works Wu et al. recently conducted an animal experiment using MK-8617, a non-selective PHDi that they administered to rats after the onset of HS [43]. The treated animals exhibited reduced lactic acidosis, improved hemodynamic parameters, and reduced prothrombin time, in addition to enhanced survival. This survival benefit was maintained after the introduction of whole blood resuscitation, demonstrating the potential value of PHDis as standalone or adjuvant treatment in conventional hemostatic resuscitation. PHDis appear to have very broad clinical potential beyond HS [49]. In trauma, Li et al. [44] showed a stimulating effect on spinal cord healing after experimental trauma in which axon regeneration was enhanced.

Use in humans PHDis were developed for the treatment of anemia in chronic renal failure and anemia resulting from chemotherapy due to their ability to stimulate the secretion of erythropoietin. Their efficacy in this indication has been established, though questions remain regarding their role in clinical practice due to the potential for long-term adverse effects [50]. In the context of HS, this molecule is not yet in clinical trials. In addition, no parenteral formulation of these compounds is currently available, which may limit their use in the treatment of severe trauma. The potential of these agents to enhance lactate clearance also renders them promising candidates for the treatment of lactic acidosis, including iatrogenic lactic acidosis [51], but there have been no ongoing clinical trials in this indication.

O-GlcNAcylation (Table 4)

Biological rationale O-GlcNAcylation (O-GlcNAc) is a post-translational modification of cytoplasmic, nuclear, and mitochondrial proteins that consists of the addition of a sugar, β-D-*N*-acetylglucosamine (or GlcNAc), to their serine and threonine residues. O-GlcNAcylation turnover is controlled by a single pair of enzymes: O-linked *N*-acetylglucosaminyltransferase (O-GlcNAc transferase or OGT) adds the GlcNAc motif to proteins, and O-linked *N*-acetyl β-D-glucosaminidase (O-GlcNAcase or OGA) removes it. OGT uses uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc), which is synthesized by the hexosamine biosynthetic pathway, as a sugar donor. Thus, O-GlcNAc can be considered a metabolic sensor. O-GlcNAc levels can be increased by either glucosamine supplementation, which stimulates the hexosamine biosynthetic pathway, or pharmacological enzyme inhibition (e.g., inhibition of OGA) [61].

This post-translational modification is involved in many, if not all, biological processes and in the development of many diseases [61]. O-GlcNAcylation of proteins also appears to play a major role in the cellular response to stress and cell survival [62, 63]. Increased levels of O-GlcNAcylation in cells before or immediately after exposure to stress (whether thermal, chemical, or hypoxic) have a protective effect by improving cell survival, whereas decreased levels have a deleterious effect [64–66]. O-GlcNAc stimulation has also

Table 4 Summary of O-GlcNAcylation stimulation testing in hemorrhagic shock models

O-GlcNAcylation stimulation				
Current use in humans	None. Only clinical trial in humans (furthest along in phase 2 in tauopathies)			
Supposed mechanism of action involved in hemorrhagic shock	O-GlcNAc level increase would be a natural response of the cell to stress			
Demonstrated effects in hemorrhagic shock	Murine model	Glucosamine supplement	Increase in mean arterial blood pressure during hemorrhagic shock	Nöt et al. 2007 [52] Zou et al. 2009 [53]
			Increased organ perfusion in kidney and brain Improved cardiac output	Yang et al. 2006 [54]
			Mitigation of lactic acidosis	Nöt et al. 2010 [55] Yang et al. 2006 [54] Zou et al. 2009 [53]
			Mitigation of IL-6 and TNF-α increase	Yang et al. 2006 [54] Zou et al. 2009 [53]
			Reduction of neutrophil activity in the heart (assessed by myeloperoxidase levels) Attenuation of nuclear factor κ B signaling pathway activation	Zou et al. 2009 [53]
		PUGNAC administration	Mitigation of lactic acidosis Mitigation of Il-6 increase Decrease in nuclear factor κ B binding activity Attenuation of organ liver during hemorrhagic shock Reduction of neutrophil activity in the lung (assessed by myeloperoxidase levels)	Nöt et al. 2010 [55]
		NButGT administration	Increase O-GlcNAc levels in the heart Restoration of mean arterial blood pressure Restoration of ionic balance (sodium and potassium) Increased Na/K ATPase activity and expression	Dupas et al. 2023 [56] Vergnaud et al. 2023 [57]
	Porcine model	None		
Demonstrated beneficial effect on survival in hemorrhagic shock	Murine model	Glucosamine supplement	Survival improvement with administration after induction of shock	Nöt et al. 2007 [52]
		PUGNAC administration	Survival improvement with administration after induction of shock	Nöt et al. 2010 [55]
	Porcine model	None		
Other effects of interest in severe trauma management	Neuroprotective effects have been described in experimental models of cerebral ischemia and hemorrhage			Wang et al. 2021[58] Jiang et al. 2017 [59] He et al. 2021 [60]

O-GlcNAc, O-GlcNAcylation; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; Na/K ATPase, sodium–potassium adenosine triphosphatase

been shown to be beneficial in sepsis, particularly for cardiac function during septic shock [67–69].

Summary of preclinical works Unlike most other stressors, cellular hypoxia induced by severe hemorrhage lowers O-GlcNAc levels in cells [70]. Several animal experiments using murine models of traumatic HS have shown that increasing these levels improves cardiac function and cerebral perfusion and reduces serum lactate levels. These results were obtained by stimulating the hexosamine pathway with a substrate (glucosamine) [54] or by using OGA inhibitors, such as PUGNAc [70]. More recently, studies using another OGA inhibitor, NButGT, have shown improvement in hemodynamic and electro-

lyte balance via O-GlcNAcylation of renal Na/K ATPase in rats exposed to HS [56, 57]. That stimulation of Na/K ATPase may be beneficial in the acute phase of HS is an old hypothesis [71].

The process of protein O-GlcNAcylation also plays a role in the inflammatory response. In the context of severe bleeding, increasing levels of O-GlcNAcylation lead to a reduction in acute inflammation by attenuating the increase in pro-inflammatory cytokines, such as TNFα or IL-6, as has been shown after trauma in animals in which O-GlcNAcylation was stimulated [52, 54, 70]. Inhibition of the NF-κB pathway by increasing levels of intracellular O-GlcNAcylation appears to be one of the mechanisms involved [53]. This effect has also been demonstrated in vascular tissue [72, 73]. In a model of endoluminal arterial injury, rats treated with glucosamine after injury had reduced inflammation, improved healing, and a clear reduction in the formation of neointima at 14 days [74].

Improvement in these biological and hemodynamic markers induced by an increase in O-GlcNAc was associated with an increase in the survival of animals. This increase in survival was observed with [55] or in the absence of resuscitation [52] in mouse models of traumatic HS. Notably, in these experiments, the treatments were initiated after the onset of shock and did not require premedication to be effective, making their use as adjuvant therapy in severe trauma plausible.

Stimulation of O-GlcNAc could also be beneficial after the acute phase by reducing secondary complications. It improves cellular tolerance to the ischemia–reperfusion lesions that develop after HS and that are responsible for secondary multi-visceral failure. The neuroprotective effects of O-GlcNAcylation have also been described in animal models of cerebral ischemia and hemorrhage [58, 59]. Stimulation of O-GlcNAcylation in a mouse model of intracerebral hemorrhage reduced the size of the hematoma, reduced the inflammatory response in the brain, and reduced the functional consequences as assessed by neurological tests [60].

Use in humans Dietary supplementation with Glucosamine has long been used in the treatment of osteoarthritis with great tolerance [75, 76], even in the long-term [77, 78]. However, its clinical effect in this indication is still controversial [79], though some trials have shown an improvement in painful symptoms, and even in radiological symptoms [80, 81]. All of these clinical trials used daily doses of glucosamine, the most common being 1500 mg/day in three doses for adults, which is lower than the amounts used experimentally to achieve a therapeutic effect in HS. Nevertheless, clinical toxicity studies conducted in humans with high doses of glucosamine (30–300 mg/kg in 6 h) have shown that glucosamine is well tolerated; it does not destabilize carbohydrate metabolism at high doses [82, 83]. This paves the way for clinical trials with higher doses of glucosamine.

Another means of acting on O-GlcNAcylation levels are OGA inhibitors. By reducing the activity of the enzyme that removes the GlcNAc moiety from proteins, OGA inhibitors increase proteins O-GlcNAcylation levels. These molecules are used experimentally both in vitro and in vivo. The molecules most commonly used in preclinical studies have not been tested in humans. Recently, however, new molecules have been developed and tested in humans. One of the most promising compounds is MK-8719, an OGA inhibitor with very high specificity developed by Selnick et al. [84]. It is currently being studied for tauopathies [85] and has entered a phase 1 trial in humans [86]. Still in favor of the therapeutic potential of O-GlcNAcylation in tauopathies, another group has developed an OGA-inhibiting molecule (LY3372689) [87] that is currently being evaluated in a phase 2 trial in humans because its safety profile was shown to be acceptable in phase 1 clinical studies [88]. These data raise hopes for clinical trials in fields other than neurodegenerative pathologies, and especially in severe trauma and HS.

Histone deacetylase inhibitors (Table 5)

Biological rationale Histones are nuclear proteins that DNA wraps around to form chromatin. Acetylation of the lysine residues on histones relaxes the chromatin, making the DNA more accessible to transcription factors. Conversely, hypoacetylation condenses chromatin and makes gene expression more difficult. This hypoacetylation of histone proteins is mediated by histone deacetylase in HS. Histone deacetylase inhibitors counteract this phenomenon and facilitate transcription dynamics, enabling the activation of mechanisms that promote cell survival [111, 112]. There are 18 histone deacetylase isoforms in humans with different actions in different tissues [113, 114]. Some inhibitors are class-specific, whereas others are nonspecific and act on several classes of histone deacetylase.

Summary of preclinical works Among the nonspecific histone deacetylase inhibitors, VPA is the most widely studied in the context of trauma. Like other nonspecific inhibitors, VPA first demonstrated its efficacy on the survival of murine models of HS as a pretreatment [115]. This effect was then confirmed when VPA was administered after the induction of shock to better match clinical practice. In murine models of lethal HS, administration of VPA and suberoyanilide hydroxamic acid, another nonspecific histone deacetylase inhibitor,

Table 5 Summary of histone deacetylase inhibitors testing in hemorrhagic shock models

Histone deacetylase inhibitors					
Current use in humans	Treatment of bipolar disorder and epilepsy (e.g., valproic acid) Preventive treatment of migraine (e.g., valproic acid) Anti-neoplasic (e.g., suberoylanilide hydroxamic acid)				
Supposed mechanism of action involved in hemorrhagic shock	Promotes chromatin decondensation, facilitating transcription mechanisms				
Demonstrated effects in hemorrhagic shock	Murine model 21/03/2025 14:01:00	Valproic acid	Protecting effect against organ damage during hemorrhagic shock:	In liver	Gonzales et al. 2006 [89] Gonzales et al. 2008[90]
				In lung	Kochanek et al. 2012 [91] Fukudome et al. 2012 [92]
				In kidney	Zacharias et al. 2011 [93]
				In heart	Wang et al. 2016 [94]
			Downregulation of transcription of genes involved in apoptosis and cell-death pathways		Zacharias et al. 2011 [93] Butt et al. 2009 [95]
		Suberoylanilide hydroxamic acid	Protecting effect against kidney damage during hemorrhagic shock Downregulates genes transcription involved in apoptosis and cell-death pathways		Zacharias et al. 2011 [93]
		Tubastatine A	Protection against lung injury during hemorrhagic shock Diminution of endotheliopathy of trauma		Bruhn et al. 2018 [96]
			Maintains mitochondria pyruvate dehydrogenase activity after hemorrhagic shock Downregulates genes transcription involved in apoptosis and cell-death pathways		Chang et al. 2015 [97]
	Porcine model	Valproic acid	Prevention of platelet dysfunction during hemorrhagic shock		Bambakidis et al. 2017 (ex vivo study) [98] Dekker et al. 2014 [99]
			Downregulation of transcription of genes involved in apoptosis and cell-death pathways in the brain		Dekker et al. 2014 [100]
			Mitigation of lactic acidosis and coagulopathy after hemorrhagic shock		Causey et al. 2013 [101] 21/03/2025 14:01:00

Table 5 (continued)

Histone deacetylase inhibitors				
Demonstrated beneficial effect on survival in hemorrhagic shock	Murine model	Valproic acid	Administrated without resuscitation, as pretreatment before hemorrhagic shock induction	Gonzales et al. 2006 [89] Gonzales et al. 2008 [90]
			Administered after hemorrhagic shock induction	Zacharias et al. 2011 [93] Shults et al. 2008 [102] Butt et al. 2009 [95] Fukudome et al. 2010 [103]
		Tubastatin A	Administered without resuscitation after hemorrhagic shock induction	Chang et al. 2015 [97]
		Suberoylanilide hydroxamic acid	Administered without resuscitation after hemorrhagic shock induction	Zacharias et al. 2011 [93]
	Porcine model	Valproic acid	Administered after hemorrhagic shock induction, during saline resuscitation	Alam et al. 2009 [89]
			Administered after hemorrhagic shock, during dried plasma resuscitation	Alam et al. 2011 [93]
			Administered after hemorrhagic shock, along with packed red blood cells	Williams et al. 2019 [104]
		ACY-1083	Administered after hemorrhagic shock, along with saline resuscitation	Biesterveld et al. 2020 [105]
Other effects of interest in severe trauma management	Valproic acid limits size of brain lesion in traumatic brain injury associated to hemorrhagic shock models			Jin et al. 2012 [106] Imam et al. 2013 [107] Nikolian et al.2017 [108] Halaweish et al. 2015 [109]
Clinical trials in human	Severe trauma	None		
	Cardiac surgery	recruiting trial To study the protective effect against organ damage during cardiac surgery (kidney and heart)		Val-CARD trial [110]

in the absence of resuscitation increased the survival rate by > 50% compared to the control group [102]. Nonselective histone deacetylase inhibitors have also been shown to have a cell protective effect during HS [91–93].

In addition, VPA has been tested in large animal models with protocols combining severe trauma and HS. Treatment with VPA improved survival compared with resuscitation with isotonic saline [89], and this effect was maintained when combined with standard resuscitation with transfusion [104]. Nonselective histone deacetylase inhibitors have been shown to improve survival in HS in murine and porcine models, either alone or in combination with standard resuscitation [116].

Although some studies have shown no efficacy of histone deacetylase inhibitors on mortality in pig models of HS [117, 118], a meta-analysis including 101 studies exploring the effect of histone deacetylase inhibitors (specific and nonspecific) on both rodents and pigs in the context of ischemia–reperfusion, sepsis, and severe trauma clearly demonstrated an effect of histone deacetylase inhibitors on the mortality of treated animals [119]. This work also demonstrated cellular protection in the heart, brain, and kidneys, reduced inflammation, and reduced apoptosis in animals treated with histone deacetylase inhibitors. Therefore, the biological effect of histone deacetylase inhibitors in the context of severe trauma is clearly accepted, but further studies are needed before clinical trials can be planned in humans. The best specific or nonspecific inhibitors, and their most appropriate dosage, need to be defined.

Use in humans VPA is the compound most likely to be tested in humans for HS in the near future because it is already authorized for and widely used in humans for the treatment of epilepsy and prevention of migraines [120]. Although the usual dosage for humans is between 20 and 30 mg/kg, doses of at least 250 mg/kg appear necessary to obtain a clinically relevant effect on HS in rat models [121]. Lower doses may be sufficient in humans given the hypermetabolism of rodents [122]. Moreover, a toxicity study carried out in healthy volunteers demonstrated good tolerance of 140 mg/kg [123]. Obviously, further studies are required in patients in shock, as the pharmacodynamics of the drug may be different in this type of patient. To the best of our knowledge, no trial is currently underway in the field of trauma, as the one listed at clinicaltrials.gov was stopped before completion due to enrollment difficulties [124]. However, a clinical trial is currently being conducted in the United Kingdom to evaluate the efficacy of VPA premedication in protecting the heart and kidneys during surgical procedures in cardiac surgery patients [110].

A systemic approach: adenosine–lidocaine–magnesium solution (Table 6)

Biological rationale

ALM solution was empirically developed for cardiac surgery as a protective solution in cardioplegia. It consists of adenosine to inhibit the sinus node, lidocaine to reduce the amplitudes of action potentials by blocking voltage-dependent sodium channels, and magnesium to stabilize the cardiomyocyte membrane. The good results observed during surgery on the heart have led to the idea of testing this solution in the context of traumatic HS by administering it systemically. The doses required when the three molecules are used together are much lower than the usual doses of each of the three drugs, suggesting a potentiation phenomenon between them. Another enigma is that the effects of ALM solution can last several hours in animal experiments, but the half-lives of the three molecules are quite short (< 1 min for adenosine and ~ 5 h for lidocaine and magnesium) [142].

Summary of preclinical works

In murine models of HS, ALM solution has resulted in a significant reduction in mortality, including when administered after the onset of shock [125, 129, 131]. The solution has also been tested in pig models of HS [133–135]. In these models, the effect on mortality was not as obvious, but multiple biological parameters were favorably modified, including hemodynamic parameters, lactate levels, and renal function. One group reported lower efficiency than conventional resuscitation using normal saline [137], but in their model, pigs were anesthetized with buprenorphine, which could have an impact on mortality [142].

Initially developed for cardioplegia, ALM solution has clear cardiovascular effects during HS. It seems to reduce vascular resistance while stimulating cardiac contractility, thereby increasing the compliance of the cardiovascular system [133]. Its action on the cardiovascular system could be partly mediated by the autonomic nervous system. Authors have described an association between the overrepresentation of parasympathetic system receptors in cardiac cells (i.e., the ratio between M2 and β-1 muscarinic receptors) and the survival of rats treated with ALM solution [131]. A reduction in exsanguination has also been reported in a mouse model [129].

ALM solution also appears to play a role in the global blood failure that occurs during HS. A study in rats with HS showed a correction of viscoelastometric parameters and prothrombin time in animals treated with ALM solution [128]. These results have been confirmed in other studies, including in pig models [130, 137]. Endotheliopathy also appears to be a target of ALM solution. In a

Table 6 Summary of adenosine–lidocaine–magnesium solution testing in hemorrhagic shock models

Adenosine–lidocaine–magnesium solution				
Current use in humans	Cardioplegia solution in cardiac surgery			
Supposed mechanism of action involved in hemorrhagic shock	Not yet really identified			
Demonstrated effects in hemorrhagic shock	Murine model	Increase in mean arterial blood pressure and other hemodynamics parameters	With no resuscitation	Letson and Dobson 2011 [125] Letson and Dobson 2011 [126] Letson et al. 2012 [127] Letson and Dobson 2015 [128] Letson et al. 2017 [129]
			With reinfusion of shed blood	Letson and Dobson 2011 [125]
		Significant decrease in PT and aPTT (return to baseline)		Letson et al. 2012 [127] Letson and Dobson 2015 [128]
		Correction of ROTEM parameters		Letson and Dobson 2015 [128] Letson et al. 2017 [130]
		Decrease in the amount of lost blood over 6 h compared to saline controls Increase in gut and kidney perfusion during shock		Letson et al. 2017 [129]
		Mitigation of anemia Prevention of the increase of plasma level of IL-1α and IL-1β, and IL-2, IL-6, and TNFα Prevention of the decrease of plasma level of fibrinogen Maintaining normal platelet aggregation (collagen and ADP-induced)		Letson et al. 2017 [130]
		Could promote dominance of the parasympathetic system in the heart during hemorrhagic shock (assessed by the ratio of M2 muscarinic receptors to β-1 adrenergic receptors), which would be associated with increased survival		Letson et al. 2022 [131]
	Porcine model	Improving in mean arterial blood pressure, cardiac output, and other hemodynamic parameters		Granfeldt et al. 2012 [132] Granfeldt et al. 2014 [133] Granfeldt et al. 2014 [134] Letson et al. 2020 [135]
		Mitigation of lactic acidosis		Granfeldt et al. 2014 [133] Granfeldt et al. 2014 [134] Letson et al. 2020 [135] Letson et al. 2019 [136]
		Reduce fluid requirement to maintain Mmean arterial blood pressure during hypotensive resuscitation		Granfeldt et al. 2012 [132]
		Increase O2 delivery to tissues		Letson et al. 2020 [135]
		Improve cardiac and kidney functions with a maintained effect after reinfusion of shed blood		Granfeldt et al. 2012 [132] Granfeldt et al. 2014 [133]
		Mitigates fibrinogen decrease and maintains ROTEM parameters		How et al. 2019 [137]
		Modification of expressions of genes involved in mitochondria function		Letson et al. 2019 [136]

Table 6 (continued)

Adenosine–lidocaine–magnesium solution			
Demonstrated beneficial effect on survival in hemorrhagic shock	Murine model	Significant improved survival compared to control; Adenosine–lidocaine–magnesium solution administrated after shock induction	Letson and Dobson 2011 [125] * Letson et al. 2017 [129] Letson et al. 2019 [136] **Maintained effect after resuscitation with shed blood*
	Porcine model	Survival gains not statistically significant	Letson et al. 2020 [135]
		Negative: Survival with Hextend and Ringer lactate solution would be greater than survival with Adenosine–lidocaine–magnesium solution	How et al. 2019 [137]
Other effects of interest in severe trauma management	Limit ischemia reperfusion injury after resuscitative endovascular balloon occlusion of the aorta in porcine models		Conner et al. 2021 [138] Franko et al. 2022 [139]
	Reduces infarction area and neurological deficits after experimental cerebral ischemia in murine model		Wang et al. 2022 [140]
	Significant reduction of mortality after moderate traumatic brain injury in murine model		Letson and Dobson, 2018 [141]
Clinical trials in human severe trauma	None		

PT, prothrombin time; aPTT, activated partial thromboplastin time; ROTEM, rotational thromboelastometry; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; IL-1α, interleukin 1α; IL-1β, interleukin 1β; IL-2, interleukin 2; ADP, adenosine diphosphate

mouse model, treatment was shown to limit the rise in syndecan-1, the main marker of endotheliopathy [141], and to help maintain glycocalyx thickness (intravital microscopy) in treated animals with HS. Finally, the cellular oxygen debt appears to be reduced by treatment. In a pig model, ALM solution reduced brain oxygen consumption, reduced the expression of hypoxia-inducible factors, and reduced venous lactate levels [135]. Finally, platelet function may be improved by ALM solution according to aggregometry studies carried out in rats with HS [130].

Although its cellular mechanisms remain unclear, ALM solution has a clear biological effect and holds promise for HS by targeting both cardiac function and blood failure in the acute phase.

Use in humans

Initially developed for this indication, ALM solution is used by cardiac surgery centers as a protective solution in cardioplegia and has shown good results [143]. ALM solution provides better myocardial protection, and the time required to resuscitate the heart post-surgery appears to be shorter when it is used [144, 145]. Each component of this solution is a drug already authorized for human use. The affordability and availability of these products, along with ALM solution use in cardiac surgery, suggest potential for clinical trials. However, none are currently underway. The incomplete understanding of its mechanisms in shock may be a contributing factor to this situation.

Discussion

Here, we presented six molecules that we consider to be particularly promising in the field of HS. This work does not claim to be exhaustive; it does not address all candidate molecules for adjuvant treatment in HS, and this is an obvious limitation. Nevertheless, we think these molecules are good candidates for future clinical trials.

The drugs presented here are promising, but most of the experiments were carried out in murine models, and less often in porcine models. Therefore, more work is needed to confirm the results in larger animals and humans. When a biological model is changed, the initial results are not always reproduced [146, 147]. A major limitation of many of the studies investigating adjuvant treatment for HS is indirect assessment of the efficacy of the molecule under investigation. Many works presented here fall into this category. Indeed, the parameters used, such as biomarkers of mitochondrial function, plasma levels of inflammatory markers, or ischemia–reperfusion lesions in organs, do not directly reflect the ability of these compounds to improve survival. Even if certain markers appear to be highly relevant (e.g., hemodynamic parameters), they remain secondary indicators that are not systematically associated with a gain in survival. Therefore, in this work, we selected molecules that have shown improved survival in animal models, which appears to be the only valuable primary endpoint. Most of these molecules have, so far, only shown survival gains in murine models (i.e., niacin, thiazolidinediones, PHDi, O-GlcNAc, and ALM solution), whereas histone deacetylase inhibitors have also shown survival gains in swine models. HS constitutes a systemic pathology, exerting its effects on the entirety of the body. In this regard, a holistic approach must be adopted when appraising novel therapeutic interventions.

Another limitation of preclinical results is the stereotypical nature of the trauma models studied. Researchers need perfectly calibrated and reproducible clinical situations to identify and dissect the biological mechanisms discovered. Despite the increasing complexity of models and use of larger models to approximate human biology, clinical trials do not always achieve the expected results. Clinical presentations are extremely diverse: traumas may be open or blunt, patients may be young or old, and they may have comorbidities and take medication. Treatment is not always comparable in terms of the time it takes to implement certain therapies or hospital access. Many factors, such as the ingestion of toxic substances, can also alter the body's response to trauma [148]. Similarly, in clinical settings, the tested molecules are to be administered to patients who have received other medications, including blood products, potentially in substantial doses. Blood transfusions in patients with severe trauma modify the cytokine environment regardless of the trauma itself [149]. Consequently, the outcomes observed for the molecules described in this study may differ in clinical trials, particularly for those involving inflammation-associated signaling pathways. For this reason, in the field of HS, many molecules are often tested first in surgical patients undergoing hemorrhagic procedures, who undergo the same surgery and are, therefore, more comparable. Similarly, studies in war-wounded soldiers, who are more comparable in terms of age, comorbidities, and time to treatment, often make it easier to draw conclusions than studies in civilian populations. Thus, caution should be exercised when drawing conclusions from preclinical work in animal models.

In the area of severe trauma, there are a number of compounds that, despite a strong preclinical base, have struggled to demonstrate a benefit in clinical trials [142, 150]. Most of the molecules presented here are already approved for human use in indications other than severe bleeding. This is the case with niacin, glitazones, glucosamine, and VPA. Thus, their toxicological profiles in humans have already been partially established. This is

the concept of "drug repurposing," which is becoming increasingly prevalent, particularly from an economic standpoint [151]. However, for the compounds we have presented here, phase 1 trials will be unavoidable. The drugs will behave differently in a severely traumatized patient. Absorption may be altered, as well as renal and/or hepatic clearance. In the case of severe bleeding, distribution factors may also be different. In addition, enzyme function may be altered in hypothermia, which is often associated with severe trauma. The other need is to determine the optimum dosage for humans suffering from trauma.

In the case of stimulating O-GlcNAcylation of proteins, inexpensive inhibitors, such as NButGT, have never been tested in humans, and those that have entered human clinical trials are still in phase 2 and for indications in chronic pathology that may have drawbacks over a long period of treatment [18]. All of this must not detract from the ethical requirements of clinical research [152], and toxicity studies will be inevitable before such molecules can be used in severe trauma patients. However, the prognosis of traumatic HS is so poor that ethics committees may consider this when deciding whether to allow a clinical trial to proceed. The risk of potential long-term side effects can be weighed against the high short-term mortality. This reasoning is quite common in major trauma and has been applied, for example, to the risks associated with the transfusion of non-Rh(D)-negative whole blood to young women of childbearing age [153]. Moreover, the short-term prognosis of severe trauma patients is poor enough to consider compassionate use of molecules that have not yet been well studied in this indication.

Conversely, if we were to develop molecules for prophylaxis, administered prior to the onset of shock, it would be imperative that no serious side effects be tolerated given that they would be administered to healthy individuals. Beyond premedication during surgery, preventive treatment could be given to certain professionals, such as soldiers or firefighters, before going on dangerous missions, as some authors envision for tranexamic acid [154].

Figure 1 shows the pathways by which the various molecules presented in this paper may affect survival in HS based on preclinical results obtained in animal models. Some molecules appear to act through multiple pathways. We can also ask whether these molecules may work in combination, potentiating one another. This is the approach adopted by the teams working on ALM solution [142] and Chu et al. [15], who tested a solution combining niacin, dichloroacetate, and resveratrol. In these two examples, the doses needed to achieve a biological effect are much lower when the molecules are used together than the usual doses of each drug used alone. Lower doses could also mean fewer side effects when translated into humans, and combining molecules increases the chances of achieving a biological effect in a genetically heterogeneous population [142].

Conclusion

Traumatic HS remains a major public health problem. Without questioning the concept of damage control resuscitation and earliest possible surgery, it is legitimate

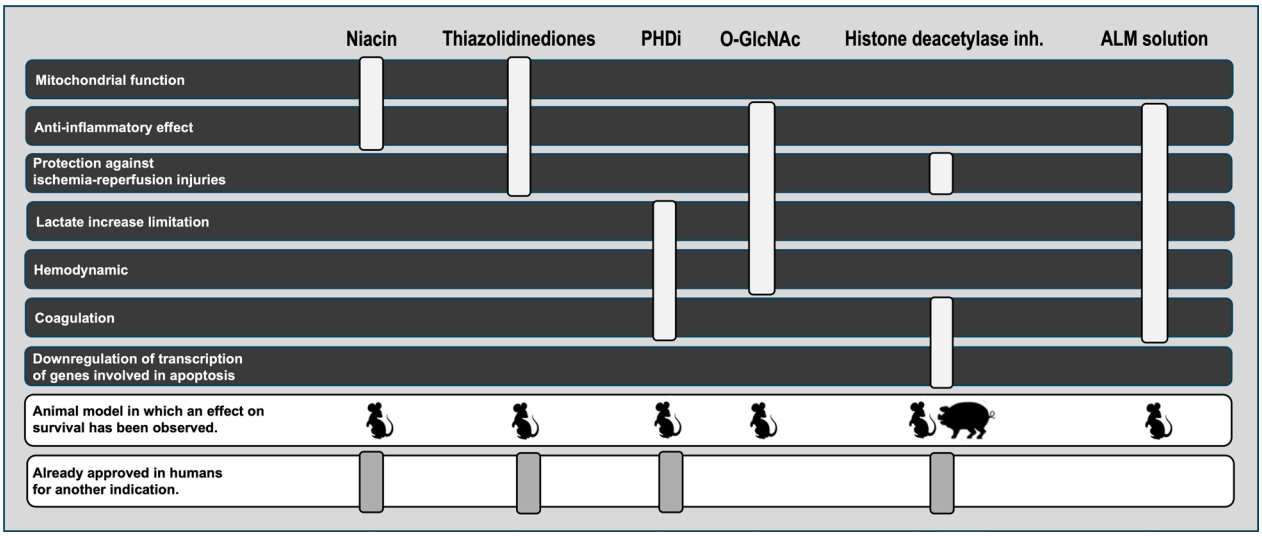

Fig. 1 Schematic representation of the potential modes of action of the different molecules according to the pre-clinical data obtained in animals. PHDi, prolyl hydroxylase domain inhibitors; O-GlcNAc, O-GlcNAcylation; Histone deacetylase inh, histone deacetylase inhibitors; ALM solution, adenosine–lidocaine–magnesium solution

to seek adjuvant treatments to increase cell survival in the acute phase and improve the prognosis of these casualties. Here, we presented compounds with clear therapeutic potential that deserve to enter clinical trials soon. However, the promising results of the preclinical studies presented here should not blind us to the frequent failures of animal-to-human translation.

Abbreviations

HS	Hemorrhagic shock
NAD	Nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
ATP	Adenosine triphosphate
TNF-α	Tumor necrosis factor alpha
MCP-1	Monocyte chemotactic protein 1
PPAR-γ	Proliferator-activated receptors gamma
PHDi	Prolyl hydroxylase domain inhibitor
HIF	Hypoxia-inducible factor
HIF-α	Hypoxia-inducible factor α subunit
O-GlcNAc	O-GlcNAcylation
Na/K ATPase	Sodium–potassium adenosine triphosphatase
VPA	Valproic acid
ALM	Adenosine–lidocaine–magnesium
IL	Interleukin
ADP	Adenosine diphosphate

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